**CHARACTERIZATION OF CORTICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR SUBTYPES.** D. E. Grigoriadis, T. W. Lovenberg, C. Liaw, D. Chalmers, E. B. DeSouza. Neurocrine Biosciences Inc., San Diego, CA 92121

Corticotropin-releasing factor (CRF) secreted by the hypothalamus is the primary regulator of the release of ACTH and other proopiomelanocortin derivatives from the anterior pituitary gland. In addition to its endocrine role, CRF has a broad extrahypothalamic distribution in brain and fulfills all of the criteria for a bona fide neurotransmitter. The cloning of the $CRF_1$, receptor, and more recently two splice forms of a second member of the CRF receptor family, designated $CRF_{2\alpha}$ and $CRF_{2\beta}$ has allowed the discrete localization of the mRNA of these receptor subtypes and has demonstrated a clear and distinct pattern of distribution in rat brain and periphery. We have expressed the $CRF_1$ and both splice forms of the $CRF_2$ receptor subtypes in stable cell lines and characterized the pharmacological and functional profiles of these proteins. $CRF_{2\alpha}$ and $CRF_{2\beta}$ receptors are both positively coupled to adenylate cyclase through a G-protein, however, they exhibit a different pharmacological profile between each other and $CRF_1$ receptors. The CRF-related peptides, r/hCRF, ovine CRF, bovine CRF, sauvagine and Urotensin I all bind and potently stimulate cAMP production in stable cell lines for $CRF_1$ and $CRF_{2\beta}$ receptors with approximately equal affinities. While sauvagine and Urotensin I exhibit the same affinity for $CRF_{2\alpha}$ receptors as $CRF_1$ and $CRF_{2b}$, r/hCRF, ovine CRF and bovine CRF, are all weaker by 10 to 100 fold for this subtype. The peptide antagonists, α-helCRF(9-41) and d-PheCRF(12-41), both inhibit CRF- or sauvagine-stimulated cAMP production with the same potency on all receptor subtypes. The differential pharmacological profile of $CRF_1$, $CRF_{2\alpha}$ and $CRF_{2b}$ receptors suggests distinctive and selective functional roles for each receptor subtype. Furthermore, the stable expression of CRF receptor subtypes in clonal cell lines represents a unique opportunity for the discovery of subtype-selective non-peptide ligands which would presumably target different aspects of CRF-mediated disorders.

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